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Particulate air pollution has been associated with adverse respiratory health effects. This study assessed the utility of expired nitric oxide to detect acute airway responses to metal-containing fine particulates. Using a repeated-measures study design, we investigated the association between the fractional concentration of expired nitric oxide (F_ENO) and exposure to particulate matter with an aerodynamic mass median diameter of ≤ 2.5 μm ($PM_{2.5}$) in boilermakers exposed to residual oil fly ash and metal fumes. Subjects were monitored for 5 days during boiler repair overhauls in 1999 (n = 20) or 2000 (n = 14). The Wilcoxon median baseline F_ENO was 10.6 ppb [95% confidence interval (CI): 9.1, 12.7] in 1999 and 7.4 ppb (95% CI: 6.7, 8.0) in 2000. The Wilcoxon median $PM_{2.5}$ 8-hr time-weighted average was 0.56 mg/m^3 (95% CI: 0.37, 0.93) in 1999 and 0.86 mg/m^3 (95% CI: 0.65, 1.07) in 2000. F_ENO levels during the work week were significantly lower than baseline F_ENO in 1999 (p < 0.001). A significant inverse exposure–response relationship between log-transformed F_ENO and the previous workday's $PM_{2.5}$ concentration was found in 1999, after adjusting for smoking status, age, and sampling year. With each 1 mg/m^3 incremental increase in $PM_{2.5}$ exposure, log F_ENO decreased by 0.24 (95% CI: –0.38, –0.10) in 1999. The lack of an exposure–response relationship between $PM_{2.5}$ exposure and F_ENO in 2000 could be attributable to exposure misclassification resulting from the use of respirators. In conclusion, occupational exposure to metal-containing fine particulates was associated with significant decreases in F_ENO in a survey of workers with limited respirator usage. *Key words:* **air pollutants, epidemiology, nitric oxide, occupational, particulate matter.** *Environ Health Perspect* **111:676–680 (2003). doi:10.1289/ehp.5880 available via *http://dx.doi.org/* [Online 31 October 2002]**

Residual oil fly ash (ROFA) is an emission source air pollutant resulting from the combustion of fuel oil. Previous epidemiologic studies have shown that exposure to ROFA particulates is associated with adverse respiratory health effects (Hauser et al. 1995a, 2001; Lees 1980; Williams 1952; Woodin et al. 2000). Individuals occupationally exposed to high levels of ROFA particulates for extended periods of time experienced a reduction in pulmonary function (Hauser et al. 1995a; Lees 1980) and frequent, severe respiratory symptoms (Woodin et al. 2000). Other studies found an increase in proinflammatory cytokines and polymorphonuclear cells in the nasal lavage fluid of these workers, indicating the presence of upper airway inflammation after ROFA exposure (Hauser et al. 1995b; Woodin et al. 1998). Although many previous studies have shown that exposure to ROFA particulates adversely affects respiratory health, few sensitive early indicators of airway response have been used in these studies.

This study evaluated the utility of expired nitric oxide (NO) to detect acute airway responses to occupational particulate exposure. Endogenous NO is produced when the enzyme NO synthase (NOS) catalyzes the conversion of L-arginine to L-citrulline and NO (Marletta 1993). Of the three types of NOS, neuronal NOS and endothelial NOS generally have constitutive activity, whereas inducible NOS is immunoactivated (Michel and Feron 1997). Endogenous NO plays a crucial role in the airways because NO is a potent neurotransmitter of bronchodilator nerves (Belvisi et al. 1992). In addition, NO produced from inducible NOS expression is important in nonspecific host defense of the respiratory tract (Moncada and Higgs 1993). Expired NO has been found to be a sensitive and noninvasive marker for the assessment of inflammatory lung diseases (Silkoff 2000). Individuals with asthma, bronchiectasis, or airway infections have increased levels of expired NO compared with healthy individuals (Kharitonov and Barnes 2000; Kharitonov et al. 1994).

The use of expired NO in the assessment of acute airway responses is not limited to the clinical setting. Previous studies have shown that various components of air pollution are associated with increased levels of expired NO (Steerenberg et al. 2001; Van Amsterdam et al. 1999). In particular, urban children experienced a significant increase in expired NO with increasing particulate and black smoke exposure (Steerenberg et al. 2001). In one animal study, exposure to diesel exhaust particles (DEP), another component of ambient air, resulted in increased expired NO in mice (Lim et al. 1998). In contrast, exposure to cigarette smoke, both active and passive, has been shown to decrease expired NO levels in epidemiologic studies (Kharitonov et al. 1995; Yates et al. 2001). Cigarette smoke has been found to reduce NO production by inhibiting NOS expression or activity (Su et al. 1998).

The measurement of expired NO has been used frequently in clinical and research settings to characterize acute airway responses, yet its use in an occupational environment has been limited. In this short-term prospective cohort study, we investigated the association between the fractional concentration of NO in mixed expired gas (F_ENO) and exposure to fine particles with an aerodynamic mass median diameter of ≤ 2.5 μm ($PM_{2.5}$) in a group of boilermakers who were performing maintenance and repairs on oil-fired boilers. The boilermakers were monitored during a 5 day work period using a repeated-measures study design. Occupational $PM_{2.5}$ exposure resulted mainly from the ROFA inside the boilers and the various work tasks of the boilermakers, which included welding and burning. ROFA and metal fumes contain significant levels of soluble transition metals such as vanadium and nickel, making their chemical compositions distinct from that of ambient air pollution or DEP. Previous studies have shown that the change in F_ENO depends on the specific type of exposure. In this study, we examined the direction of change in F_ENO to metal-containing fine particulates.

Materials and Methods

Study population. The study was approved by the Institutional Review Board of the Harvard School of Public Health. Written informed consent was obtained from each subject. The study population consisted of 32 boilermakers working at a power plant during the overhaul

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of oil-fired boilers. Twenty subjects were monitored in June 1999, and 14 subjects, including two from 1999, were monitored in October 2000. Self-administered questionnaires were used to obtain information on medical history, including respiratory symptoms and diseases, smoking history, and occupational history.

F_ENO collection. F_ENO samples were collected before and after work shifts each day during a 5-day sampling period. Baseline F_ENO samples were collected before the work shift on the first day of the work week, after 1–2 days away from work. The offline collection and measurement of F_ENO were in accordance with American Thoracic Society (ATS) recommendations (ATS 1999). Subjects were asked to refrain from smoking in the 1 hr preceding NO sampling. Subjects wore nose clips and tidal breathed for 30 sec through an apparatus containing two one-way valves with a NO-scrubbing filter attached to the intake limb to prevent sample contamination by ambient NO. Subjects then inhaled to total lung capacity and expired their entire vital capacity into a Mylar balloon attached to the expiratory limb while maintaining an oropharyngeal pressure of 12.5 cm H_2O. Three F_ENO samples were taken at each collection time. To minimize NO loss in the Mylar balloons, we measured the NO levels within 4 hr of sample collection. NO levels in the balloons were measured using a calibrated Sievers (Boulder, CO) NOA 280 chemiluminescence analyzer. The median NO concentration of the three samples was used in the statistical analysis because it was insensitive to any aberrant observations while providing a measure of central value.

Spirometry. Spirometry was conducted before the work shift on the first and last day of sampling using a MicroPlus spirometer (Micro Direct Inc., Auburn, ME). Subjects performed a minimum of three acceptable forced vital capacity (FVC) maneuvers. The reproducibility standards required that the two highest forced expiratory volume in 1 sec (FEV_1) values be within 10% or 0.2 L of each other. The highest FEV_1 and FVC values from any of the maneuvers were used in the analysis.

Exposure assessment. Subjects were randomly selected to wear personal exposure monitors (PEMs) during their work shift. Workplace particulate samples were collected from 19 of the 20 subjects in 1999 and from all 14 subjects in 2000. The number of workdays each subject wore the PEM varied from 5 study days to none. On average, each subject was monitored 2 to 3 times throughout the week. The model 200 PEM (MSP Corp., Minneapolis, MN) with a 2.5 µm impactor cutsize was used in line with a Gilian GilAir5 pump (Sensidyne Inc., Clearwater, FL) calibrated at a flow rate of 4 L/min. The air sample was collected on a polytetrafluoroethylene membrane filter (Gelman Laboratories, Ann Arbor, MI) placed within the PEM. The PEMs were placed on the lapels of the subjects, near their breathing zone. The mass collected on the filter was divided by the air volume sampled to calculate the gravimetric $PM_{2.5}$ concentration.

Statistical analysis. Statistical analyses were performed using SAS version 6.12 (SAS Institute Inc., Cary, NC) and S-Plus2000 for Windows (MathSoft Inc., Cambridge, MA). Two-sample *t*-tests and Wilcoxon rank-sum tests were performed to compare the baseline characteristics of the population in the 2 sampling years. Paired *t*-tests were performed to compare prework F_ENO and spirometry values from baseline (day 1) to day 5 of sampling, days where corresponding F_ENO and spirometry measurements were both collected. The strength of the association between the changes in prework F_ENO and the changes in spirometric values from baseline to day 5 was determined using the Spearman rank correlation coefficient.

Linear models were constructed to investigate the association between log-transformed F_ENO values and $PM_{2.5}$ exposure. A linear model with independent and identically distributed errors was used because the repeated within-subject F_ENO measurements were found to be uncorrelated (Kleinbaum et al. 1998). Although F_ENO data collection was complete, $PM_{2.5}$ concentration data were missing. However, the $PM_{2.5}$ sampling data were missing at random because subjects were randomly selected each day to wear exposure monitors. Therefore, all analyses were restricted to subjects who had both F_ENO and the corresponding $PM_{2.5}$ concentrations on a given day. Including baseline data, there were a total of 50 complete measurements in 1999 and 46 complete measurements in 2000. F_ENO values were log-transformed to improve normality. The models were adjusted for self-reported current cigarette smoking status (yes/no), age, and sampling year. In addition, an interaction term between sampling year and $PM_{2.5}$ exposure was included in the model. The level of significance for all analyses was 0.05.

Results

Description of study population. Population demographic data are summarized in Table 1. The study population consisted of 32 men, 31 of whom were white (97%). Thirteen of the 32 subjects (41%) were current cigarette smokers. Their ages ranged from 18 to 59 years, with 2 weeks to 40 years of boilermaking experience. Twenty subjects were sampled in 1999, and 14 subjects, including two that were monitored in 1999, were sampled in 2000. Of the 32 subjects, six subjects entered the cohort on the second day of sampling because they had not attended work the previous day. Three subjects dropped out of the study after the fourth day of sampling; two subjects were transferred to a different work shift, and one subject did not come to work on the last day of sampling.

Six of the 32 subjects (19%) had chronic obstructive pulmonary disease (COPD), as defined by ATS (1995). Five subjects had chronic bronchitis, as diagnosed by a physician or with symptoms as defined by ATS (1995). One subject had emphysema diagnosed by a physician. None of the subjects with COPD were on medications that could influence expired NO levels. All analyses were performed initially with the total cohort, and then analyses were rerun after excluding the subjects with COPD. Because the results from the two analyses did not differ significantly, the final results included all 32 subjects.

The baseline spirometry results are summarized in Table 1. Only subjects with reproducible FEV_1 on both days that spirometry was performed were included in the spirometry analyses. None of the demographic information was significantly different between those who had reproducible spirometry and

Table 1. Study population characteristics by sampling year.

Study population characteristics	1999	2000
Number of subjects	20	14[a]
Number (%) of current smokers	9 (45%)	5 (36%)[b]
Number (%) of subjects with COPD	4 (20%)	2 (14%)
Age, years		
Mean ± SD	45.4 ± 12.0	41.5 ± 11.1
Range	18–59	20–55
Years as boilermaker		
Mean ± SD	21.7 ± 12.9	17.4 ± 13.5
Range	0.04–40	0.08–36
Number (%) of subjects with complete spirometry data[c]	14 (70%)	9 (64%)
Mean ± SD baseline percent predicted FEV_1[c,d]	95.8 ± 11.3	92.8 ± 9.2
Mean ± SD baseline percent predicted FVC[c,d]	95.4 ± 14.6	93.6 ± 8.1
Mean ± SD baseline percent FEV_1/FVC[c]	79.5 ± 7.0	79.3 ± 9.9

[a]Includes two subjects that were also monitored in 1999. [b]Includes one subject that was also monitored in 1999. [c]Includes only subjects with reproducible spirometric values on both days that spirometry was performed. [d]Spirometric predictions were based on predicted normal values by Hankinson et al. (1999).

those who did not. The mean baseline percent predicted FEV_1 was 95.8% (SD 11.3) in 1999 and 92.8% (SD 9.2) in 2000. The mean baseline percent predicted FVC was 95.4% (SD 14.6) in 1999 and 93.6% (SD 8.1) in 2000. The mean baseline percent predicted FEV_1 and FVC values were not statistically different in the two sampling years ($p > 0.2$).

Baseline measurements of F_ENO. The baseline measurements of F_ENO are shown in Table 2. Baseline measurements were taken on average after 2 days away from work in 1999 and 1 day away from work in 2000. Wilcoxon confidence intervals (CIs) and corresponding medians are presented because of the positively skewed distribution of F_ENO. In the 1999 cohort, the median baseline F_ENO was 8.8 ppb (95% CI: 7.0, 13.6) for smokers and 12.2 ppb (95% CI: 9.8, 15.9) for nonsmokers. In the 2000 cohort, the median baseline F_ENO was 7.6 ppb (95% CI: 6.5, 8.3) for smokers and 7.4 ppb (95% CI: 6.2, 8.6) for nonsmokers. The median baseline F_ENO across the two sampling years was significantly different for nonsmokers ($p = 0.002$) but not for smokers ($p < 0.20$).

Exposure assessment. The occupational $PM_{2.5}$ exposures for the 1999 and 2000 survey periods are shown in Table 3. The mean sampling time was 8.8 hr (SD 1.2) in 1999 and 10.9 hr (SD 1.3) in 2000. The difference in the average time monitored in the two sampling years was due to the difference in work shift length. During the overhaul in 1999, the boilermakers worked 10-hr shifts, whereas in 2000 most of the boilermakers worked 12-hr shifts. To account for this difference in work shift length, $PM_{2.5}$ concentrations were standardized to 8-hr time-weighted averages (TWAs). The Wilcoxon median $PM_{2.5}$ 8-hr TWA was 0.56 mg/m^3 (95% CI: 0.37, 0.93) in 1999 and 0.86 mg/m^3 (95% CI: 0.65, 1.07) in 2000. The median $PM_{2.5}$ 8-hr TWAs were marginally different in the two sampling years ($p = 0.06$).

In 1999, 85% of the subjects stated in the questionnaires that they wore respirators while performing boiler maintenance and repair. However, it was noted by the field team that the actual use of respirators while working was limited because of the high temperatures and limited ventilation inside the power plant. Data from the National Weather Service, Boston Weather Forecast Office (Taunton, MA), indicated that the maximum temperature in Boston, Massachusetts, was 92°F (33°C) to 97°F (36°C) during the first half of the 1999 sampling period. In the 2000 sampling period, 85% of the subjects also stated that they wore respirators while working. In contrast to 1999 observations, the field team observed that respirator use was more common in 2000. The maximum temperature in Boston during the 2000 sampling period ranged from 53°F (12°C) to 65°F (18°C). The cooler temperature may have made use of respirators more tolerable. The respirators typically used were the half-mask particulate respirators equipped with a high-efficiency particulate air (HEPA) filter, which has a particle filter efficiency of 99.97% for particles with an aerodynamic mass median diameter of 0.3 μm (NIOSH 1996).

Changes in F_ENO and spirometric parameters. The changes in F_ENO and spirometric parameters after occupational particulate exposure were calculated as the difference in the prework measurements from baseline (day 1) to day 5 of sampling. Measurements from day 5 were used to compare with the baseline levels because day 5 was the only workday during which both spirometry and F_ENO samples were collected. The changes in F_ENO and spirometric measurements are shown in Table 4. The mean change in F_ENO was –5.5 ppb (95% CI: –8.8, –2.1) for 1999 subjects and +1.0 ppb (95% CI: –0.2, 2.2) for 2,000 subjects. The changes in F_ENO for each individual are shown in Figure 1.

A similar trend was seen in the mean change in FEV_1 and FVC. The mean change in FEV_1 was –0.17 L (95% CI: –0.24, –0.09) for 1999 and –0.05 L (95% CI: –0.19, 0.09) for 2000. Likewise, the mean change in FVC was –0.14 L (95% CI: –0.23, –0.04) for 1999 subjects and +0.02 L (95% CI: –0.18, 0.22) for 2000 subjects. Compared with baseline levels, the F_ENO, FEV_1, and FVC values were significantly lower on day 5 in the 1999 subjects ($p < 0.01$). In contrast to 1999 data, the F_ENO, FEV_1, and FVC values from day 5 did not differ statistically from the baseline measurements in 2000. The changes in F_ENO, FEV_1, and FVC values did not differ by smoking status.

Baseline-adjusted changes were used to determine the correlation between F_ENO and spirometric parameters. In both 1999 and 2000, the changes in F_ENO were significantly correlated to the changes in FEV_1 ($r = 0.51$, $p = 0.01$) and moderately correlated with changes in FVC ($r = 0.39$, $p = 0.07$).

Association between F_ENO and $PM_{2.5}$ exposure. There was a weak correlation between $PM_{2.5}$ 8-hr TWA exposure and the postshift F_ENO on the same day ($r = –0.06$, $p = 0.60$). Furthermore, the linear models did not indicate a significant association between postshift F_ENO and the $PM_{2.5}$ exposure from the same day after adjusting for preshift F_ENO. However, there was a stronger lagged association between preshift F_ENO and $PM_{2.5}$ exposure from the previous workday ($r = –0.22$, $p = 0.03$). Therefore, analyses were restricted to regressing preshift F_ENO on $PM_{2.5}$ exposure the previous day.

Linear models indicated that $PM_{2.5}$ exposure was associated with a decrease in log F_ENO in the sampling year 1999. With each 1 mg/m^3 increase in $PM_{2.5}$ exposure, log F_ENO decreased by 0.24 (95% CI: –0.38, –0.10) after adjusting for dichotomized cigarette smoking status, age, and sampling year. Cigarette smoking was significantly associated

Table 2. Baseline F_ENO measurements (ppb) by sampling year and cigarette smoking status.

Sampling year	No. subjects	Median[a]	95% CI
1999	20	10.6	(9.1, 12.7)
Current smokers	9	8.8	(7.0, 13.6)
Nonsmokers[b]	11	12.2	(9.8, 15.9)
2000	14	7.4	(6.7, 8.0)
Current smokers	5	7.6	(6.5, 8.3)
Nonsmokers[b]	9	7.4	(6.2, 8.6)

[a]Wilcoxon median. [b]Nonsmokers include ex-cigarette smokers and never smokers.

Table 3. Occupational $PM_{2.5}$ exposure by sampling year.

	1999	2000
Number of samples	30	33
Mean ± SD sampling time, hr	8.8 ±1.2	10.9 ±1.3
$PM_{2.5}$ 8-hr TWA, mg/m^3		
Median[a]	0.56	0.86
95% CI	(0.37, 0.93)	(0.65, 1.07)

[a]Wilcoxon median.

Table 4. Changes in F_ENO and spirometric parameters from baseline (day 1) to day 5 by sampling year.[a]

	1999 ($n = 14$)[b] Mean (95% CI)	2000 ($n = 9$)[b] Mean (95% CI)
Change in F_ENO (ppb)	–5.5 (–8.8, –2.1)	+1.0 (–0.2, 2.2)
Change in FEV_1 (L)	–0.17 (–0.24, –0.09)	–0.05 (–0.19, 0.09)
Change in FVC (L)	–0.14 (–0.23, –0.04)	+0.02 (–0.18, 0.22)

[a]Change = day 5 – day 1. [b]n = number of subjects. Includes only subjects with complete data (F_ENO and reproducible spirometric values on both days 1 and 5).

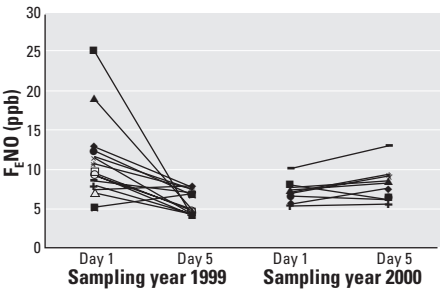

Figure 1. F_ENO measured on day 1 (baseline) and day 5 of the monitoring period by sampling year. The F_ENO values on day 1 were significantly different from those on day 5 in sampling year 1999 ($p < 0.001$) but not in 2000 ($p > 0.3$).

with a change of –0.22 (95% CI: –0.36, –0.08) in log F_ENO. Residual analysis indicated that there were two subjects with standardized residuals greater than 2. After excluding the two potential statistical outliers, log F_ENO decreased by 0.19 (95% CI: –0.32, –0.05) for each 1 mg/m^3 of $PM_{2.5}$ exposure. Although the two outlying subjects increased the magnitude of the association between $PM_{2.5}$ exposure and log F_ENO, their influence was marginal.

For the subjects sampled in year 2000, there was no association between $PM_{2.5}$ exposure on the previous workday and preshift log F_ENO. After adjusting for cigarette smoking status, age, and sampling year, the $PM_{2.5}$ regression coefficient was 0.02 (95% CI: –0.15, 0.18).

Discussion

In the present study, short-term occupational exposure to particulates was associated with a significant decrease in F_ENO and spirometric indices. A significant inverse exposure–response association between log F_ENO and $PM_{2.5}$ 8-hr TWA exposure was found. However, these associations were seen only in subjects tested in 1999. In the group of boilermakers sampled in 2000, there was no change in F_ENO or spirometric indices, and no exposure–response relationship between log F_ENO and $PM_{2.5}$ exposure.

A possible explanation for the lack of change in F_ENO and spirometric parameters, and lack of an exposure–response relationship between $PM_{2.5}$ exposure and F_ENO in the 2000 subjects could be attributable to respirator use. During the sampling week in June 1999, temperatures neared 100°F (38°C) inside the power plant because of a heat wave and limited ventilation. The difficult environmental conditions might have prevented the boilermakers from wearing their respirators. In contrast, the climate was much cooler during the sampling period in October 2000, making the use of respirators more tolerable. Because the half-mask respirators used by the boilermakers had a particle filter efficiency greater than 99% for particles with an aerodynamic mass median diameter of 0.3 μm, respirator use would have significantly decreased the exposure to particulates during the sampling year 2000. The reduced particulate exposure might explain the lack of a difference between baseline F_ENO, FEV_1, and FVC measurements and measurements taken during the work week in 2000.

During both sampling years, the PEMs were placed on the lapels of the subjects, near their breathing zones. Based on observations made in 1999, no modifications were made in the exposure assessment procedure to adjust for respirator use in 2000. Because the subjects in 2000 were more likely to wear respirators, the $PM_{2.5}$ measurements during this sampling year were less likely to represent true exposure. The $PM_{2.5}$ measurement error might be responsible for the lack of an exposure–response relationship between $PM_{2.5}$ and F_ENO in 2000. We were unable to estimate the effect of respirator use on $PM_{2.5}$ exposure because usage was inconsistent and the fit of the respirators was unknown because of factors such as the presence of facial hair.

Changes in F_ENO from baseline to day 5 were strongly correlated with changes in FEV_1 ($r = 0.51$, $p = 0.01$) and moderately correlated with changes in FVC ($r = 0.39$, $p = 0.07$) in subjects from both sampling years 1999 and 2000. Other studies have also examined the relationship between F_ENO and spirometric indices. Jones et al. (2001) showed a negative correlation between changes in F_ENO and changes in FEV_1 ($r = –0.35$, $p < 0.002$) across weeks. The conflicting results between the Jones et al. study and our study may be attributable to the difference in the study populations. The population in our study generally consisted of healthy subjects, whereas Jones et al. studied asthmatics. The relationship between expired NO and FEV_1 may be dependent on the subjects' states of airway inflammation. Although an increase in F_ENO indicates loss of asthma control in asthmatics (Kharitonov et al. 1994; Massaro et al. 1996), a decrease in F_ENO from normal levels in healthy individuals may be considered an adverse response, as in the case of smokers (Kharitonov et al. 1995). In the present study, a decrease in F_ENO was associated with a decrease in FEV_1, both adverse respiratory responses in healthy individuals.

In our study, a significant inverse exposure–response association between the previous workday's $PM_{2.5}$ 8-hr TWA exposure and the next day's preshift log F_ENO was found in the subjects in 1999. With the median $PM_{2.5}$ exposure of 0.56 mg/m^3, F_ENO declined by 13% from baseline after adjusting for current cigarette smoking status, age, and sampling year.

Previous studies have shown that particulate air pollution is associated with an increase in expired NO levels (Steerenberg et al. 2001; Van Amsterdam et al. 1999). In a study by Steerenberg et al. (2001), exposure to particulate air pollution was associated with an increase in F_ENO. Although the results of our study are inconsistent with the results from Steerenberg et al., there are several important differences in the two studies. First, Steerenberg et al. used particulate matter with an aerodynamic mass median diameter of ≤ 10 μm (PM_{10}) as the marker for particulate exposure, whereas we used $PM_{2.5}$. Our study chose $PM_{2.5}$ because fine particles have been found to have a stronger association with respiratory health effects than coarse particles with larger aerodynamic mass median diameters (Schwartz and Neas 2000). Another difference between the studies is that Steerenberg et al. studied the effects of particulate exposure from urban air pollution, whereas we studied the effects of particulates from ROFA and various boilermaking tasks such as welding and burning. Unlike ambient air, ROFA and metal fumes contain significant amounts of transition metals, including vanadium, nickel, and iron. In addition, the levels of exposure from the two aerosols were different. Typical urban air has a $PM_{2.5}$ concentration of approximately 10–30 μg/m^3, whereas the median $PM_{2.5}$ level from the occupational particulate exposure in our study was 560 μg/m^3.

Other studies have observed that exposure to DEP, another component of ambient air, was associated with increased expired NO levels in mice (Lim et al. 1998; Sagai and Ichinose 1995). Lim et al. found that DEP exposure increased the level of constitutive NOS in the airway epithelium and inducible NOS in the macrophages of mice. However, another study observed that DEP reduced endothelial NOS activity in the bronchi of healthy rabbits (Muto et al. 1996). The source of the increased NO is relevant because the effect of NO may differ depending on whether it is produced by inducible or constitutive NOS. Takano et al. (1999) showed that NO produced from inducible NOS might enhance the DEP-induced inflammatory response, whereas NO derived from constitutive NOS might play a protective role against airway inflammation.

Exposure to cigarette smoke also is known to induce acute airway inflammation. However, in contrast to the results from air pollution and DEP, cigarette smoking consistently results in decreased expired NO levels (Kharitonov et al. 1995; Yates et al. 2001). One hypothesis for the reduction in expired NO is that the levels of NOS are reduced from decreased transcription of NOS. A study by Su et al. (1998) observed that cigarette smoke specifically affected constitutive NOS activity. After exposure to cigarette smoke extract, the presence of endothelial NOS and endothelial NOS mRNA was reduced in the pulmonary artery endothelial cells from pigs. The decrease in endothelial NOS activity caused by cigarette smoke extract was found to be time and dose dependent.

A recent study by Huang et al. (2002) found that ROFA instilled intratracheally into isolated perfused rabbit lungs resulted in reduced NO production, as determined by decreases in nitrite/nitrate accumulation. Huang et al. also observed that NO production was reduced after exposure to vanadium, indicating that the transition metal component of ROFA may be responsible for the decreased NO production. Huang et al.

hypothesized that the inhibition of NO production by ROFA might be related to reduced NOS activity, as shown in studies with cigarette smoke exposure. Therefore, the decrease in F_ENO observed in the boilermakers in our study might be due to a reduction in constitutive NOS activity resulting from ROFA and other metal-containing fine particulate exposure. Given the potential protective role of NO from constitutive NOS, the decreased NO levels might have been a contributing factor to the increased airway inflammation and respiratory symptoms seen in our previous studies on boilermakers exposed to ROFA and other particulates (Hauser et al. 1995a; Woodin et al. 2000).

In conclusion, we found an inverse exposure–response relationship between F_ENO and $PM_{2.5}$ in exposed workers. The results from our study show greater consistency with the studies on exposure to cigarette smoke than to those of ambient air pollution. Cigarette smoke contains a significant concentration of transition metals, similar to ROFA and metal fumes (Chiba and Masironi 1992; Dreher et al. 1997). Further studies are needed to determine if the metal component of $PM_{2.5}$ is specifically responsible for the decline in F_ENO.

Expired NO previously has been found to be a sensitive and practical marker in the assessment of inflammatory lung diseases in a clinical setting. This study shows that F_ENO can be used to detect acute airway responses to metal-containing fine particulate matter in an occupational setting.

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